NASA Procedural Requirements

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COMPLIANCE IS MANDATORY

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Request Notification of Change (NASA Only)

Subject: Care and Use of Animals (updated w/Change 2 on 3/20/14)

Responsible Office: Office of the Chief Health & Medical Officer

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Appendix F: Optional Supporting Material for the Vertebrate Animal Science Review (VASR)

Detailed Instructions for Preparation of the VASR Worksheet
These instructions are to assist applicants in preparing their VASR information.

Preparation of the VASR worksheet:
Typically, all of the required elements for the VASR can be addressed within 1-2 pages.

Point 1 - Description of animals and how they will be used
A concise, complete description of the proposed procedures must be included in the VASR. While additional details may be included in the Research Strategy, a coherent, albeit brief, description of the proposed use of the animals must be provided within the VASR. The description must include sufficient detail to allow evaluation of the procedures. Examples of the types of procedures that should be described include blood collection, surgical procedures, administration of substances, tumor induction, and post-irradiation procedures. In describing the animals, investigators must provide the following information for each species and/or strain to be used:
• Species
• Strain
• Ages
• Sex
• Number of animals to be used

Point 2 - Justifications for use of animals
Investigators must justify the use of animals in the proposed research. The justification must indicate why alternatives to animals (e.g., computer models, cell culture) cannot be used and should indicate the potential benefits and knowledge to be gained. In addressing this point, researchers are encouraged to consider means to replace, reduce, and refine the use of animals. Rationale for the choice of species must be provided. The rationale should indicate the advantages of the species chosen and why alternative species are not appropriate. If less highly evolved or simpler animal models are available, justification must be provided for using more advanced species. For example, the use of non-human primates (NHP), dogs, or cats should be thoroughly justified. If NHP species are to be used, a comparison to other NHP species may be appropriate. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and the number of animals used.

Estimates for the number of animals to be used should be as accurate as possible. Justification for the number of animals to be used should include considerations of animal availability, experimental success rate, inclusion of control groups and requirements for statistical significance. Cite power calculations, where appropriate.

Point 3 - Veterinary care
Descriptions of veterinary care should indicate the availability of veterinarians or veterinary technicians. For example, the VASR might indicate the number of veterinarians and veterinary technicians associated with the applicant institution and their proximity to the performance site(s). The frequency with which veterinary staff observe

or monitor animals should be stated. If survival surgeries are proposed, veterinary involvement or post-surgical monitoring should be described. For example, if animal use involves invasive approaches that might result in discomfort, distress, or pain, the investigator should indicate if or when veterinary care is necessary. The indicators for veterinary intervention to alleviate discomfort, distress, or pain should be described. The ways in which veterinary staff may intervene should be described.

Point 4 - Provisions to minimize discomfort, distress, pain, and injury
Procedures or circumstances that may result in more than momentary discomfort, distress, pain, or injury should be identified. Methods to alleviate discomfort, distress, or pain should be described. If pharmacological agents are used, the agent(s) should be specified by name or class. Any additional (e.g., non-pharmaceutical) means to avoid discomfort, distress, pain, or injury should be described briefly. The manner, circumstances, and duration of all post-surgical provisions and care should be described. If special housing is necessary following surgery or manipulations, the VASR should describe these provisions, the duration and type of monitoring provided. If procedures (e.g., pharmacological or surgical) might lead to severe discomfort, distress, pain, or injury indicators for humane endpoints and euthanasia (e.g., severe infection, respiratory distress, failure to eat, tumor size) should be described. All of these issues are particularly important for survival surgeries. If multiple surgeries are proposed, these must be well justified and provisions to avoid any potential complications must be described. Describe how restraining devices will be used, if applicable.

Point 5 - Euthanasia
The method(s) of euthanasia must be described and must comply with the AVMA Guidelines on Euthanasia. If the method(s) do not comply with AVMA recommendations, the rationale and scientific justification for use of the method(s) must be provided. The indicators for euthanasia (i.e., termination of experiment or humane endpoints) should be stated. It is not sufficient to state simply that humane methods will be used, that are consistent with the recommendations of the AVMA Guidelines on Euthanasia or the Institutional Animal Care and Use Committee (IACUC).

References
Guidance in this document is based on NASA and PHS Policy, and Federal requirements. The NASA and PHS Policy incorporate the standards in the Guide for the Care and Use of Laboratory Animals and require that euthanasia be conducted according to the AVMA Guidelines on Euthanasia. Additional background information and references are available from the Office of Laboratory Animal Welfare, National Institutes of Health (available on-line).

NASA Policy and Requirements

NASA Policy Directive 8910.1 - Care of Use of Animals (available on-line i the NASA NODIS library).
NASA Procedural Requirements 8910.1 - Care of Use of animals (available on-line i the NASA NODIS library).

PHS Policy

Public Health Policy on Humane Care and Use of Laboratory Animals, Office of Laboratory Animal Welfare, National Institutes of Health, 2002 (available on-line).

Guide for the Care and Use of Laboratory Animals, Eighth Edition, Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research Division on Earth and Life Studies, National Academies Press, Washington, DC, 20011(available on-line).

AVMA Guidelines on Euthanasia

AVMA Guidelines for the Euthanasia of Animals: 2013 Edition, American Veterinary Medical Association, 2013, (available on-line).

Checklist to Assist in Addressing the Required Five Points of the VASR

Performance site(s):

The five points must be addressed for all performance sites.

__ If the applicant's institution is not where animal work will be performed, are all collaborative performance site(s) identified?

__ If more than one performance site is planned, are descriptions of animal care and use for each site provided?

Point 1 - Describe the animals and their proposed use; address the following for all species to be used:
__ Species.
__ Strains.
__ Ages.
__ Sex.
__ Number of animals to be used.

__ A concise, but complete, description of proposed procedures (i.e., sufficient information for evaluation).

Point 2 - Provide justifications for:
__ The use of animals.
__ Choice of species.
__ Number of animals to be used (cite power calculations, if appropriate).

Point 3 - Provide a general description of veterinary care, including veterinary support that is specifically relevant to the proposed procedures. Indicate the following:
__ A brief account of veterinary staff and their availability.
__ The regular schedule of monitoring of animals by veterinary staff.
__ Any additional monitoring and veterinary support that may be required to ensure humane care, if relevant to the procedures proposed (e.g., post-surgical).
__ Indicators for veterinary intervention to alleviate discomfort, distress, and/or pain, if relevant.

Point 4 - Describe procedures to minimize discomfort, distress, pain, and injury. Indicate the following:
__ Circumstances relevant to the proposed work, when animals may experience discomfort, distress, pain, and/or injury.
__ Procedures to alleviate discomfort, distress, pain, and/or injury.
__ Identify (by name or class) any tranquilizers, analgesics, anesthetics, and other treatments (e.g., antibiotics) and describe their use.
__ Provisions for special care or housing that may be necessary after experimental procedures.
__ Plans for post-surgical care, if survival surgeries are proposed.
__ Indicators for humane experimental endpoints, if relevant.
__ Describe the use of restraint devices, if relevant.

Point 5 - Describe methods of euthanasia:
__ Describe the method(s) of euthanasia and rationale for selection of method(s).
__ Indicate if the method is consistent with AVMA Guidelines on Euthanasia.
__ Provide a scientific justification for the choice of method, if not AVMA recommended.

Example of a complete VASR Worksheet

(This VASR worksheet has been modified from the original. It addresses all five points concisely.)

Vertebrate Animals
Aims 1-3 will be addressed in vitro; Aim 4 will be addressed using a mouse model of ocular infection.

1. Female Balb/c mice will be used to determine if virions treated with enzyme can cause viral keratitis, and to test the in vivo efficacy of the test articles. The studies will require 700 mice, four to six weeks old. Based on prior experience, 70 groups, each including 10 mice will be required over five years to achieve adequate statistical power. Ocular infection is accomplished by scratching the cornea of anesthetized mice with a sterile needle and exposing the scarred portion of the cornea to inoculum. Test articles are applied directly to the scarified cornea as liquid or cream. Following inoculation and recovery, mice are monitored for 30 days. With the mice under anesthesia, the eyes will be examined at intervals, microscopically, and are flushed with medium with 2% serum to determine viral titers. Thirty days post-infection, with the mice under deep anesthesia, the trigeminal ganglia are removed aseptically for viral assay, followed immediately by euthanasia.

2. The proposal is to study mechanisms for the prevention of ocular disease caused by viral infections, a leading cause of blindness in the U.S. Mice are needed for these experiments because no alternative in vitro model incorporates all elements of the mammalian ocular immune system; too little is known about this system for the development of computer simulations. Mice are a well-accepted model for studying viral keratitis, assessing the virulence of viral strains and testing the efficacy of antivirals. Mice provide several advantages: a) The murine ocular immune system is similar enough to that of humans to allow extrapolation of the results, b) Their small size allows the use of smaller amounts of drugs for testing, c) The entire mouse genome is known and easily manipulated genetically, allowing extension of the work in future genetic studies. Female mice will be used due to compatibility issues. Balb/c mice will be used because they have intermediate resistance to infection. ABC-4 knockout and ABC-4 test-strains will be used. For the enzyme study, we will use four treatment groups: enzyme-1, enzyme-2, enzyme-3, and mock treated virus. We will also use different amounts of inoculum for each condition allowing a more accurate calculation as to the effect of the digestions on infectivity. For the test-article peptide study, we will use two formulations (one aqueous and one hydrophobic), test four different concentrations, and also vary the treatment protocol. Two groups will receive a single dose of drug in each of the two formulations prior to the addition of virus to assess prophylactic activity. These groups will not receive any additional enzyme treatments. Two groups will be infected with virus and beginning 4 h post-infection, we will treat with each formulation and concentration, four times daily for seven days.

3. All mice are housed in the Animal Resources Center of the University. Animal housing rooms are under temperature and humidity control. The mice will not be subjected to water or food restrictions, and bedding material

is placed in each cage. The facility is staffed by four full time veterinarians and six veterinary technicians; the veterinary staff is on site and a clinical veterinarian is available at all times. Animal care staff conducts routine husbandry procedures (e.g., cage cleaning, feeding, and watering) and checks animals daily to assess their condition. Laboratory staff monitors mice when treatments are given, disease is scored or samples are collected for titering. The veterinary staff monitors mice in their home cages, weekly. If animals exhibit any indication of infection or distress, the veterinary staff confers with laboratory personnel to recommend appropriate antibiotics, analgesics, or other pharmaceuticals. The veterinary staff may intervene or recommend euthanasia based on animal welfare concerns.

4. Mice will be anesthetized with isoflurane (3-5%) during the infection process, when treatments are administered and titer samples are collected. This eliminates the need for restraint devices and topical anesthetics that would interfere with the infection and disease process. For post-procedural pain relief, we will administer buprenorphine twice daily for the duration of the experiments (i.e., approximately two weeks post-inoculation). Death is not an endpoint for the studies; the Balb/c strain was chosen because of its resiliency and resistance to this particular virus. Our goal is to avoid severe infections leading to death. Though unlikely, if an animal reacts severely, it will be euthanized, based on humane indicators (e.g., failure to groom or feed). These experiments involve no post-surgical survival animals.

5. All mice will be euthanized by cervical dislocation under isoflurane anesthesia. Isoflurane ensures that the mice are unconscious, while dislocation ensures quick death. This minimizes animal distress, is effective and efficient; it is consistent with the recommendations of the AVMA Guidelines on Euthanasia.

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